PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day/month/year) 11 September 2000 (11.09.00)	
International application No. PCT/EP00/00130	**Applicant's or agent's file reference** BAXR/ P22173PC
International filing date (day/month/year) 07 January 2000 (07.01.00)	**Priority date** (day/month/year) 29 January 1999 (29.01.99)
Applicant MAZZA, Mario et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   14 August 2000 (14.08.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Manu Berrod
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Dee, Ian
ERIC POTTER CLARKSON
Park View House
58 The Ropewalk
Nottingham NG1 5DD
GRANDE BRETAGNE

S.E

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ACKNOWLED

RECEIVED
DEC - 4 2000
RENAL LAW

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	18.10.2000
REPLY DUE	**within 3 month(s)** from the above date of mailing

Applicant's or agent's file reference	International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
BAXR/P22173PC	PCT/EP00/00130	07/01/2000	29/01/1999

International Patent Classification (IPC) or both national classification and IPC

A61M1/16

Applicant

BIEFFE MEDITAL, S.P.A ET AL

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29/05/2001.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Bichlmayer, K-P

Formalities officer (incl. extension of time limits)
Edel, M
Telephone No. +49 89 2399 2426

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-8	as originally filed

Claims, No.:

1-6,7 (part)	as originally filed			
7 (part),8-10	as received on	14/08/2000	with letter of	11/08/2000

Drawings, sheets:

1/2,2/2	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,10 (NO)
Inventive step (IS)	Claims	1-8,10 (NO)
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separat sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Ad section V:

1) Independent claim 1

Independent claim 1 does not meet the requirements of Art. 33(2) PCT because its subject-matter lacks novelty for the following reasons:

Reference is made to the following documents:

D1: EP,A,0 278 100 (cited in the application and herewith introduced)
D2: WO,A,9 211 046

D1 describes a cartridge comprising an openable, sealed inlet and an openable, sealed outlet (cf. Fig. 7) and containing a quantity of concentrate powder such as sodium bicarbonate (cf. on page 10, line 4 to 9). Nowhere in the description of D1 it is explicitly mentioned that the internal space of the cartridge being filled with said quantity is flushed with an inert gas (such as nitrogen) so one has to assume that additionally air is present within the cartridge. As air naturally contains carbon dioxide at a certain amount, said cartridge further contains carbon dioxide as required in claim 1. Thus, D1 discloses a cartridge comprising all the features defined in claim 1 and, consequently, the subject-matter claimed lacks novelty against D1.

The subject-matter of claim 1 also lacks an inventive step, contrary to Art. 33(3) PCT with respect to D1 and D2 for the following reasons:

D2 discloses a dialysate production system comprising a hopper or magazine from which pellets containing sodium bicarbonate and citric acid are dispensed into one of two mixing chambers both of which containing a predetermined amount of water (cf. on page 3, first paragraph). As can be seen from page 4, third paragraph, citric acid in the pellets regulates the pH of the dialysate to pH 7.4 or below so that the mixture of conventional dialysate chemicals will dissolve quickly and completely in the time required by the system wherein formation of insoluble precipitates is also prevented.

Starting from D2, the subject-matter of claim 1 is distinguished over this prior art in that it comprises a cartridge rather than a hopper in combination with a mixing chamber thus simplifying the apparatus needed to produce dialysate liquid. As the skilled person would obviously take into account D1 when looking for a solution of the problem above, it appears that claim 1 lacks an inventive step.

Starting from D1 as closest prior art, claim 1 is distinguished from D1 in that sodium bicarbonate additionally comprises a solid acid wherein this combination is known from D2 having the effect of pH lowering which allows completely and timely solubilization of the solid concentrate when it comes in contact with water. As the skilled person knows that sodium carbonate present in sodium bicarbonate will better dissolve when the pH is lowered, he will obviously consider D2 such that claim 1 lacks an inventive step.

2) Independent claim 7

Claim 7 also lacks an inventive step over D1 and D2 for the same reasons set out for claim 1. Starting from D1 it is regarded as obvious for a skilled person to consider an acid additive to sodium bicarbonate (cf. D2) in order to prepare a solid dialysate concentrate which is able to regulate the pH of the dialysate such that the solid components dissolve quickly and completely in the time required. Thus, claim 7 does not meet the requirements of Art. 33(3) PCT.

3) Dependent claims 2 to 6, 8 and 10

The features of the dependent claims 2 to 6 are considered either as known from the prior art (cf. claim 3 known from D2) or obvious measures be taken by the skilled person such that these claims do not meet the requirements of Art. 33(3) PCT. With regard to dependent claim 8 the method claimed further specifies the cartridge which is however known from D1. Consequently, claim 8 is not in accordance with Art. 33(3) PCT. In-line connection of the cartridge of D1 is already known from this prior art document such that claim 10 lacks novelty and inventive step for the reasons mentioned under point 1)

above.

In order to overcome the objections, the applicant could file an amended set of claims based on the essential feature of dependent claim 9.

Ad section VII:

1) The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

2) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

Ad section VIII:

Dependent claim 4 is unclear (Art. 6 PCT) with respect to the term "another organic acid".

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference BAXR/P22173PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/00130	International filing date *(day/month/year)* 07/01/2000	Priority date *(day/month/year)* 29/01/1999
International Patent Classification (IPC) or national classification and IPC A61M1/16		
Applicant BIEFFE MEDITAL, S.P.A ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/08/2000	18.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bichlmayer, K-P Telephone No. +49 89 2399 2977

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/00130

I. Basis f the r p rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-8	as originally filed				
Claims, No.:					
1-10	as received on	18/01/2001	with letter of	18/01/2001
Drawings, sheets:					
1/2,2/2	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Ad section V:

Reference is made to the following documents:

D1: EP,A,0 278 100 (cited in the application)
D2: WO,A,92/11046

1) Independent claim 1

D1 is considered to represent the closest prior art disclosing a cartridge to be used in an in-line dialysis system which comprises a cartridge according to the features of the preamble of the independent claim 1. To adjust the pH-value of the final dialysis solution, a liquid concentrate containing acid can be introduced into a bicarbonate solution produced in said cartridge.

The subject-matter of said claim is distinguished from D1 in that the cartridge additionally contains an acid or acid anhydride or carbon dioxide gas in an amount to prevent a temporary increase in pH of a dialysis solution produced utilising the cartridge. As effect of the presence of the acid in the cartridge the pH-value of the bicarbonate concentrate is adjusted from the very beginning and no separate liquid acid is needed.

Thus, the problem to be solved by the present invention can be considered as providing a simple buffer system for a dialysis cartridge to be used in-line within a dialysis machine.

None of the available prior art documents discloses or suggests the solution provided by the distinguishing features. Although D2 describes chemical pellets containing for example bicarbonate and citric acid for the preparation of a dialysis liquid, said pellets are used for a batch process and are solubilized within a cartridge but transferred from a storage chamber into water containing mixing tanks. Since D1 and D2 concern different modes of producing a dialysis liquid (in-line vice versa batch) there is no incentive for the skilled person to consider D2 when looking for a solution of the problem discussed above. Even the skilled person would combine D1 and D2, he

would either replace said cartridge by the storage chamber wherein bicarbonate then would be introduced into a water containing mixing tank and then acid would be added, or, starting from D2, he would fed water into the storage chamber wherein the skilled person could not expect that the problem above would be solved due to different solubilities of the chemical compounds involved.

Thus, the subject-matter of the independent claim 1 meets the requirements of Art. 33(2) to (4) PCT.

2) Dependent claims 2 to 6

The dependent claims 2 to 6 meet also the requirements of Art. 33(2) to (4) insofar as they are dependent from claim 1.

3) Independent claim 7

The method of independent claim 7 also meets the requirements of Art. 33(2) to (4) PCT since the novel and inventive concept defined in claim 1 is used therein.

4) Dependent claim 8

Dependent claim 8 concerns a specific embodiment of the inventive idea of claim 7 and therefore also meets the requirements set out in Art. 33(2) to (4) PCT.

5) Claims 9 and 10

Claim 9 specifies a specific source of carbon dioxide to be used in the cartridge according to claims 1 to 6 and meets therefore also Art. 33(2) to (4) PCT. The subject-matter of claim 10 is also considered to be novel and inventive according to the requirements of Art. 33(2) to (4) PCT since the cartridge according to claims 1 to 6 is included therein.

Ad section VII:

1) The description should have be brought into conformity with the claims.

2) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

Claims:

1. A cartridge having an openable, sealed inlet and an openable, sealed outlet for connection in-line in a haemodialysis machine for passage of water or a solution through the cartridge, the cartridge containing sodium bicarbonate in solid form,

characterised in that the cartridge additionally contains an acid or acid anhydride in solid form or carbon dioxide gas in an amount to prevent a temporary increase in pH of a dialysis solution produced utilising the cartridge.

2. A cartridge according to Claim 1, wherein the acid is in powder form.

3. A cartridge according to Claim 1 or Claim 2, wherein the acid is citric acid.

4. A cartridge according to Claim 1 or Claim 2, wherein the acid is tartaric acid, or another organic acid.

5. A cartridge according to any one of the preceding claims containing at least 0.2g of acid, acid anhydride, or carbon dioxide per 1000g of sodium bicarbonate.

6. A cartridge according to Claim 5, wherein the cartridge contains at least 0.5g of acid, acid anhydride, or carbon dioxide per 1000g of sodium bicarbonate.

7. A method of preventing a temporary increase of pH in a dialysis solution being continuously produced in a haemodialysis machine from different component sources including a cartridge containing solid sodium

AMENDED SHEET

bicarbonate, th method comprising including in the cartridge an acid or acid anhydride in solid form, or carbon dioxide gas.

8. A method according to Claim 7, wherein the cartridge and its contents are in accordance with any one of Claims 1 to 6.

9. A method of introducing carbon dioxide gas to a cartridge according to Claim 1, wherein the carbon dioxide is introduced as dry ice.

10. A haemodialysis machine comprising a cartridge as claimed in any one of Claims 1 to 6 which is connected in-line.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Dee, Ian
ERIC POTTER CLARKSON
Park View House
58 The Ropewalk
Nottingham NG1 5DD
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.04.2001
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
BAXR/P22173PC	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/00130	07/01/2000	29/01/1999

Applicant
BIEFFE MEDITAL, S.P.A ET AL

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Nilles, F Tel.+49 89 2399-2931

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BAXR/P22173PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/00130	International filing date *(day/month/year)* 07/01/2000	Priority date *(day/month/year)* 29/01/1999
International Patent Classification (IPC) or national classification and IPC A61M1/16		
Applicant BIEFFE MEDITAL, S.P.A ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ *Non-establishment of opinion with regard to novelty, inventive step and industrial applicability*
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/08/2000	18.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bichlmayer, K-P Telephone No. +49 89 2399 2977

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-8	as originally filed				
Claims, No.:					
1-10	as received on	18/01/2001	with letter of	18/01/2001	
Drawings, sheets:					
1/2,2/2	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Ad section V:

Reference is made to the following documents:

D1: EP,A,0 278 100 (cited in the application)
D2: WO,A,92/11046

1) Independent claim 1

D1 is considered to represent the closest prior art disclosing a cartridge to be used in an in-line dialysis system which comprises a cartridge according to the features of the preamble of the independent claim 1. To adjust the pH-value of the final dialysis solution, a liquid concentrate containing acid can be introduced into a bicarbonate solution produced in said cartridge.

The subject-matter of said claim is distinguished from D1 in that the cartridge additionally contains an acid or acid anhydride or carbon dioxide gas in an amount to prevent a temporary increase in pH of a dialysis solution produced utilising the cartridge. As effect of the presence of the acid in the cartridge the pH-value of the bicarbonate concentrate is adjusted from the very beginning and no separate liquid acid is needed.

Thus, the problem to be solved by the present invention can be considered as providing a simple buffer system for a dialysis cartridge to be used in-line within a dialysis machine.

None of the available prior art documents discloses or suggests the solution provided by the distinguishing features. Although D2 describes chemical pellets containing for example bicarbonate and citric acid for the preparation of a dialysis liquid, said pellets are used for a batch process and are solubilized within a cartridge but transferred from a storage chamber into water containing mixing tanks. Since D1 and D2 concern different modes of producing a dialysis liquid (in-line vice versa batch) there is no incentive for the skilled person to consider D2 when looking for a solution of the problem discussed above. Even the skilled person would combine D1 and D2, he

would either replace said cartridge by the storage chamber wherein bicarbonate then would be introduced into a water containing mixing tank and then acid would be added, or, starting from D2, he would fed water into the storage chamber wherein the skilled person could not expect that the problem above would be solved due to different solubilities of the chemical compounds involved.

Thus, the subject-matter of the independent claim 1 meets the requirements of Art. 33(2) to (4) PCT.

2) Dependent claims 2 to 6

The dependent claims 2 to 6 meet also the requirements of Art. 33(2) to (4) insofar as they are dependent from claim 1.

3) Independent claim 7

The method of independent claim 7 also meets the requirements of Art. 33(2) to (4) PCT since the novel and inventive concept defined in claim 1 is used therein.

4) Dependent claim 8

Dependent claim 8 concerns a specific embodiment of the inventive idea of claim 7 and therefore also meets the requirements set out in Art. 33(2) to (4) PCT.

5) Claims 9 and 10

Claim 9 specifies a specific source of carbon dioxide to be used in the cartridge according to claims 1 to 6 and meets therefore also Art. 33(2) to (4) PCT. The subject-matter of claim 10 is also considered to be novel and inventive according to the requirements of Art. 33(2) to (4) PCT since the cartridge according to claims 1 to 6 is included therein.

Ad section VII:

1) The description should have be brought into conformity with the claims.

2) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
BAXR/P22173PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 00130	07/01/2000	29/01/1999
Applicant		
BIEFFE MEDITAL, S.P.A ET AL		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The abstract is changed as follows:

Line 1,2,4 after "cartridge" insert "(10)".

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]P 00/00130

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M1/16 A61K33/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 11046 A (UNIV WASHINGTON) 9 July 1992 (1992-07-09) page 2, line 36 -page 4, line 9; figure 2 ---	1-8
X	EP 0 177 614 A (TOMITA PHARMA) 16 April 1986 (1986-04-16) page 4, paragraph 1 -page 5, paragraph 1 ---	1-8
X	EP 0 417 478 A (NIKKISO CO LTD ;TOWA PHARMACEUTICAL CO LTD (JP)) 20 March 1991 (1991-03-20) page 2, line 1 -page 3, line 22 ---	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2000	26/04/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Zeinstra, H

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]EP 00/00130

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199118 Derwent Publications Ltd., London, GB; Class B05, AN 1991-128481 XP002135441 & JP 03 066621 A (NIKKISO CO LTD), 22 March 1991 (1991-03-22) abstract	1-8
X	WO 94 25084 A (BAXTER INT) 10 November 1994 (1994-11-10) page 6, line 4 - line 25	1-8
A	WO 97 02056 A (ALTHIN MEDICAL AB ;CARLSSON PER OLOV (SE); GILLERFALK BJOERN (SE);) 23 January 1997 (1997-01-23) page 1, line 5 - line 18 page 4, line 14 - line 29; figure 1	1,7,9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]EP 00/00130

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9211046 A	09-07-1992	CA 2098839 A	19-06-1992
		AU 7171091 A	22-07-1992
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		DE 69027052 T	26-09-1996
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		JP 11508469 T	27-07-1999
		SE 9502397 A	04-01-1997
		US 6036858 A	14-03-2000

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European Patent Office
Erhardtstraße 27
D-80298 München
GERMANY

18 January 2001

Sent by fax

Dear Sirs

International Patent Application No PCT/EP00/00130
BIEFFE MEDITAL, S.P.A. ET AL
Our ref: BAXR/P22173PC

This is a response to the written opinion dated 18 October 2000.

Amendments

We enclose a new set of claims on which the further examination of this application should be based.

Present claim 1 has been amended to state that the acid, acid anhydride or carbon dioxide gas is present in an amount to prevent a temporary increase in pH of a dialysis solution produced utilising the cartridge. Basis for this amendment can be found at page 3, lines 4 to 8, page 5, lines 12 to 17, and in claim 7 of the application as filed.

Novelty over EP-A-0278100 (D1)

The cartridge defined in new claim 1 is clearly novel over that disclosed in D1, since any carbon dioxide that might have been introduced into the D1 cartridge as a result of conducting the manufacturing process in an air atmosphere will not have been sufficient to prevent a temporary increase in the pH of a dialysis solution produced utilising the cartridge. Indeed, the acid, acid anhydride or carbon dioxide gas contained in the presently

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claimed cartridge was specifically introduced to overcome the problem with known sodium bicarbonate cartridges, such as the cartridge disclosed in D1, which tend to give rise to a high pH reading at the beginning of the dialysis procedure. The present applicant observed this problem, determined the cause of the problem and developed the presently claimed cartridge as a solution.

Inventive step in view of D1 and WO-A-92/11046 (D2)

D1 discloses a cartridge containing solid sodium bicarbonate powder having an openable, sealed inlet and an openable, sealed outlet for connection in-line in a haemodialysis machine. The cartridge is connected to the haemodialysis machine and is used for the continuous preparation of the dialysis solution that is used in the machine.

D2 discloses an *in-situ* dialysate production system for supplying dialysate directly to a haemodialysis machine. The system uses a dry chemical tablet comprising an acid, a base and a salt. The acid is separated from the base, typically by the salt. The pellets are added to mixing chambers containing treated water to form the dialysate which is then conducted into the dialysate circuit of the haemodialysis machine. Both the base and the salt can be a bicarbonate such as sodium bicarbonate. The tablets can also be preloaded into a magazine or cassette.

Although D2 discloses pre-packing the chemical tablets into a magazine or cassette, it does not disclose a cassette having an openable sealed inlet and an openable sealed outlet for connection in-line in a haemodialysis machine. Indeed, an inlet and outlet of this type in the cassette disclosed in D2 would be completely redundant, because the pellets are ultimately dispensed from the cassette and mixed with sterile water in a separate mixing tank to produce the dialysis solution for the haemodialysis machine. Thus, the magazine or cassette disclosed in D2 is simply a means of storing a plurality of tablets which are then individually dispensed into the mixing tank where they are dissolved in sterile water to form the dialysis solution.

In summary, D2 relates to a system for batch preparation of a dialysis solution in which all the dialysis solution that is required for a dialysis

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treatment is made up at the beginning of the procedure in the mixing chamber and then gradually fed to the haemodialysis machine.

The Examiner considers that it would have been obvious to modify the sodium bicarbonate containing cartridge disclosed in D1 by incorporating an acid in view of the teaching in D2. We respectfully disagree.

There is no teaching or even suggestion in D1 or D2 that would lead the person skilled in the art to modify the sodium bicarbonate cartridge disclosed in D1 so that it also contained an acid in solid form in an amount to prevent a temporary increase in pH of a dialysis solution produced using the cartridge. Neither is there any teaching that would lead the person skilled in the art to place the dry chemical tablet disclosed in D2 in a liquid flow through cartridge having an openable sealed inlet and an openable sealed outlet for connection in-line in a haemodialysis machine.

For example, it is evident from D1 that any acid in the final dialysis solution that is produced should be introduced separately as a component of a liquid concentrate (see page 10, lines 52 to 55, page 11, lines 5 to 13, and page 11, line 33, to page 12, line 20). Thus, the teaching in D1 is to add any acid separately and not to combine it with the sodium bicarbonate. This, of course, is hardly surprising because D1 fails to recognise any problem with sodium carbonate contaminating the sodium bicarbonate.

The skilled person would not dispense with the separate liquid acid concentrate used in D1 when D1 teaches that this is a necessary feature of the dialysis system disclosed in D1 and fails to suggest any potential problems with such a system that might lead the skilled person to modify the system. D1 thus teaches away from the present invention because the skilled person would conclude that the solid sodium bicarbonate and acid components should be separately charged to the water stream to produce the final dialysis solution.

D2, on the other hand, only contemplates the use of the dry chemical tablet it discloses in association with a haemodialysis system in which the required quantity of dialysis fluid for a dialysis treatment is prepared in a batch fashion at the beginning of the dialysis procedure by dissolving the tablet in a mixing chamber containing treated water.

cont/....

There is no teaching or even suggestion in D2 that the chemical tablet it discloses could be used in combination with a liquid flow through cartridge of the type disclosed in D1 for the continuous preparation of a dialysis solution which is charged to the haemodialysis machine immediately after it is made.

Continuous preparation of a dialysis solution can bring with it problems that would not be encountered in the batch wise preparative method of D2. For example, how do you overcome the differential solubility in water of the various components making up a dialysis solution when contained in a single tablet. In the batch method disclosed in D2, this is not a problem since you simply continue with the mixing process until all the solid tablet has dissolved. However, with continuous preparation using a liquid flow through cartridge, the different solubilities of the components could give rise to compositional shifts in the dialysis solution. Thus, it is clearly incorrect to say that the skilled person would be motivated to use the tablets disclosed in D2, designed for batch wise preparation of a dialysis solution, in the cartridge disclosed in D1 that is used for the continuous preparation of a dialysis solution.

In summary, D1 teaches that liquid flow through cartridges containing powdered sodium bicarbonate can be used for the continuous preparation of a dialysis solution in a haemodialysis machine that contains a separate source of liquid acid concentrate. D2, on the other hand, teaches that multi-component chemical tablets containing all the components for a dialysis solution are useable in haemodialysis machines equipped with mixing chambers in which all the dialysis solution for a dialysis treatment is prepared batch-wise at the beginning of the procedure by dissolving the tablets in treated water contained in the mixing chambers. Nothing in D1 or D2 suggests that multi-component tablets are useable in liquid flow though cartridges, and it would not be obvious to try such tablets in a liquid flow through cartridge when neither D1 nor D2 refer to any problems that would lead the skilled person to consider such an adaptation.

We submit that the presently claimed cartridge is clearly novel and

cont/....

inventive over D1 and D2 and that a favourable International Preliminary Examination Report should be issued. However, if the Examiner is still of the view that the claims lack novelty and/or inventive step, then we request that a further written opinion is issued.

Yours faithfully
ERIC POTTER CLARKSON

Ian M Dee imd/smr

Enc: Claims

Claims:

1. A cartridge having an openable, sealed inlet and an openable, sealed outlet for connection in-line in a haemodialysis machine for passage of water or a solution through the cartridge, the cartridge containing sodium bicarbonate in solid form,

characterised in that the cartridge additionally contains an acid or acid anhydride in solid form or carbon dioxide gas in an amount to prevent a temporary increase in pH of a dialysis solution produced utilising the cartridge.

2. A cartridge according to Claim 1, wherein the acid is in powder form.

3. A cartridge according to Claim 1 or Claim 2, wherein the acid is citric acid.

4. A cartridge according to Claim 1 or Claim 2, wherein the acid is tartaric acid, or another organic acid.

5. A cartridge according to any one of the preceding claims containing at least 0.2g of acid, acid anhydride, or carbon dioxide per 1000g of sodium bicarbonate.

6. A cartridge according to Claim 5, wherein the cartridge contains at least 0.5g of acid, acid anhydride, or carbon dioxide per 1000g of sodium bicarbonate.

7. A method of preventing a temporary increase of pH in a dialysis solution being continuously produced in a haemodialysis machine from different component sources including a cartridge containing solid sodium

bicarbonate, the m[redacted]d comprising including in the c[redacted]idge an acid or acid anhydride in solid form, or carbon dioxide gas.

8. A method according to Claim 7, wherein the cartridge and its contents are in accordance with any one of Claims 1 to 6.

9. A method of introducing carbon dioxide gas to a cartridge according to Claim 1, wherein the carbon dioxide is introduced as dry ice.

10. A haemodialysis machine comprising a cartridge as claimed in any one of Claims 1 to 6 which is connected in-line.